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Organization  
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(21) International Application Number: PCT/US2004/008629  
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(71) Applicant (for all designated States except US): PHARMACIA CORPORATION [US/US]; Global Patent Department, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017-1732 (US).

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(75) Inventors/Applicants (for US only): FRANCZYK, Thaddeus, S. II [US/US]; Pfizer Global Research and Development, Chemical R & D, 7000 Portage Road, Mailstop 0200-091-201, Portage, Michigan 49001 (US). WAGNER, Grace, M. [US/US]; 219 Papin Avenue, Webster Groves, MO 63119 (US).

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STEROID SPIROLACTONIZATION

(57) Abstract: A steroid comprising a 17-spirolactone or corresponding open lactone structure is obtained by carbonylation of a 17-alkenyl or 17-alkynyl substrate. A 17-alkenyl intermediate may be prepared by semi-hydrogenation of a 17-alkynyl group. Multiple reaction schemes are disclosed for preparation of a 3-keto-9,11-epoxy-17-spirolactone steroid such as eplerenone. Novel intermediates are also disclosed, as well as steps for forming such novel intermediates, or converting them to further intermediates or products, by semi-hydrogenation, carbonylation, 6,7-dehydrogenation, furylation or other transformations or combinations thereof.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
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(43) International Publication Date  
7 October 2004 (07.10.2004)

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(21) International Application Number:  
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WO 2004/085458 A3

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/08629

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(7) : C07J 1/00, 21/00 US CL : 540/41; 552/633, 637 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 540/41; 552/633, 637  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) REGISTRY, CAPLUS, CASREACT, USPATFULL		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WUTS et al., A Novel Synthesis of Spironolactone. An Application of the Hydroformylation Reaction. J. Org. Chem., 13 October 1989, Vol. 54, No. 21, pages 5180-5182, see the entire article, especially page 5181. Scheme Ia.	1-7
X	FUKUTA et al., Synthesis of 3-silyl-2(5H)-furanone by rhodium-catalyzed cyclocarbonylation. Tetrahedron Letters, 12 February 2001, Vol. 42, No. 7, pages 1301-1304, see the entire article, especially page 1304, Scheme 6.	1-7
Y	US 5,276,023 A (MOGUILEWSKY et al.) 04 January 1994 (04.01.1994), see col. 10, lines 5-12.	6
Y	US 5,236,913 A (BERGINK) 17 August 1993 (17.08.1993), see col. 2, lines 45-49.	6
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
<b>* Special categories of cited documents:</b>		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 04 October 2005 (04.10.2005)	Date of mailing of the international search report <b>28 OCT 2005</b>	
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer <i>J. Roberts for</i> Barbara P. Badio, Ph.D. Telephone No. 571-272-1600	

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/08629

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-7

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US04/08629

### BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-7, drawn to a process for preparing a 17-spirolactone steroid compound.

Group II, claim(s) 8 and 9, drawn to steroid derivatives substituted in the 17-position by a 17-alkenyl and/or alkynyl group and a 17-oxy group.

Group III, claim(s) 10 and 11, drawn to a process for preparing a steroid derivative substituted in the 17-position by a 17-alkenyl and/or alkynyl group and a 17-oxy group.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The compounds encompassed by Groups I-III contain a steroid ring system which does not define a contribution over the prior art. The substituents and definitions of variables vary extensively and, when taken as a whole result in vastly different compounds. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper.

## PATENT COOPERATION TREATY

30

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ROEDEL, John, K., Jr.  
Senniger, Powers, Leavitt & Roedel  
#1 Metropolitan Square, 16th Floor  
St. Louis, Missouri 63102  
United States of AmericaDate of mailing (day/month/year)  
27 September 2005 (27.09.2005)Applicant's or agent's file reference  
PHA4152.1

## IMPORTANT NOTIFICATION

International application No.  
PCT/US2004/008629International filing date (day/month/year)  
22 March 2004 (22.03.2004)

## 1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

HAIFENG, Wu  
3681 Fawn Cove #3  
Portage, MI 49024  
United States of America

EPO-DG 1

12. 10. 2005

TEAM 14

State of Nationality

CN

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

## 3. Further observations, if necessary:

The person identified in Box 2 has been added to the record as applicant for the United States of America only and inventor for all designated States.

## 4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned  
☒ the International Searching Authority ☒ the elected Offices concerned  
☒ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

S. Diot

Facsimile No. (41-22) 338.70.80

Telephone No. (41-22) 338 9608

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Teleprinter No.

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☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

HAVENS, Jeffrey, L.  
22570 6th Avenue  
Mattawan, MI 49071  
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

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34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

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<input type="checkbox"/> the agent	<input type="checkbox"/> the common representative
Name and Address	State of Nationality
	State of Residence
	Telephone No.
	Facsimile No.
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:	
<input type="checkbox"/> the person	<input type="checkbox"/> the name
<input type="checkbox"/> the address	<input type="checkbox"/> the nationality
<input type="checkbox"/> the residence	
Name and Address	State of Nationality
	State of Residence
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Name and Address

PEARLMAN, Bruce, Allen  
3411 Willow Lake Drive #308  
Kalamazoo, MI 49008  
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

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Name and Address MACKEY, Sonia, S. 1335 Simpson Street Saint Paul, MN 55108 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
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